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10/612,894	07/07/2003	James M. Hagberg	108172-00097	7034

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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
12/11/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/612,894	HAGBERG ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 21-29* is/are pending in the application.

4a) Of the above claim(s) *21-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18, and 21-29 are pending.
Claims 21-27 remain withdrawn as detailed in the previous Office Action of 11/15/2006.
Claims 1-18, 28, and 29 are examined on the merits

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office Action is in reply to Applicants' correspondence of 08/06/2009.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is **FINAL**.

Withdrawn Claim Rejection - 35 USC § 101 Non-Statutory Subject Matter

1. The rejection of claims under 35 U.S.C. 101 as directed to non-statutory subject matter, as set forth on pages 2-6 of the Office Action of 02/06/2009, is **WITHDRAWN** in light of the amendments to the claims.

Maintained Claim Rejections - 35 USC § 112 1st ¶ - Scope of Enablement With New Grounds As Necessitated by Amendment

2. Claims 1-18, 28, 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (with regard to claim 1):

> A method of decreasing the level of tissue plasminogen activator (t-PA) antigen in a human subject, said method comprising:
> a) obtaining a biological sample from said subject, said biological sample comprising nucleic acids from said subject;
> b) detecting in said nucleic acids at least one 4G allele of the plasminogen activator inhibitor-1 (PAI-1) gene promoter; and
> c) engaging the human subject in exercise training
> wherein the level of t-PA antigen in the human subject is decreased after said exercise training.

and (with regard to claim 28):

> A method of increasing the level of t-PA activity in a human subject, said method comprising:
> a) obtaining a biological sample from said subject, said biological sample comprising nucleic acids from said subject;
> b) detecting in said nucleic acids a homozygous 4G allele genotype of the plasminogen activator inhibitor-1 (PAI-1) gene promoter; and
> c) engaging the human subject in exercise training
> wherein the level of t-PA activity in the human subject is increased after said exercise training.

does not reasonably provide enablement for a methods wherein a PAI-1 genotype is detecting in a sample by using a protein sample, as specifically recited in the claims.

Nature of the Invention and Breadth of the Claims

The specification asserts that the instant invention relates to identifying genetic markers that correlate with improved success in increasing fibrinolysis levels in subjects through exercise training (paragraph [0003]) and provides an example in which several surrogate measures of fibrinolysis are provided (i.e.: PAI-1 activity; t-PA activity; and t-PA antigen). The claims are drawn to methods requiring advising a subject to engage in exercise training for a period of time sufficient to decrease the level of t-PA antigen (claims 1-6) or increase the level of t-PA activity (claims 28 and 29), and encompass methods of preventing cardiovascular disease (claims 7-12) and ameliorating cardiovascular disease (claims 13-18 and 29). The claims are specifically drawn to genotype detection methods in protein samples.

The nature of the invention requires knowledge of a period of time of exercise training sufficient to decrease the level of t-PA antigen (where any such decreased level of t-PA may prevent or ameliorate cardiovascular disease) or increase t-PA activity, as

well as methods wherein protein samples could be used to determine promoter genotype.

Direction provided by the specification and working example

The specification teaches an example in which subjects were analyzed for several parameters indicative of fibrinolysis levels (i.e. PAI-1 and t-PA activities and t-PA antigen (paragraph [0031])) prior to participation in an exercise program to establish baseline values, and then after participation in an exercise program (paragraph [0045]).

The specification further teaches the genotyping of the PAI-1 gene promoter with respect to the 4G/5G polymorphic site (paragraph [0042]) by PCR amplification followed by restriction enzyme analysis of the resulting amplicon.

The instant specification provides an analysis of the changes in the measured parameters among the three possible (4G/4G; 4G/5G; 5G/5G) PAI-1 genotypes. The specification indicates that the data provided is an analysis after moderate exercise training for six months (paragraphs [0047], [0048]). The data indicate the following results: the average PAI-1 activity decreased for the 4G/4G and 5G/5G groups, and increased for the 4G/5G group; the average t-PA activity increased for all groups; the average t-PA antigen decreased for all groups. The specification asserts that there is a tendency for subjects with 4G/4G genotypes to respond better than subjects with 4G/5G or 5G/5G genotypes (paragraph [0048]), the analysis of the data (P ANOVA) indicates that none of the changes are statistically significant.

The specification asserts that improving fibrinolysis prevented the development of cardiovascular disease or alleviated symptoms of cardiovascular disease (paragraph

[0007]). There is no indication that either of these two qualities was actually measured in any of the analyzed subjects; Example 1 indicates that subjects were in fact excluded from the study if they had cardiovascular disease.

The specification does not provide any protein based methods to determine PAI-1 promoter genotype.

State of the art, level of skill in the art, and level of unpredictability

The level of skill in the art with regard to identification of PAI-1 gene promoter and t-PA genotypes is high, however the prior art and the instant specification shows that the level of unpredictability in correlating any particular period of time of exercise training sufficient to prevent or ameliorate cardiovascular disease is even higher. Furthermore, there is nothing in either the instant specification or the prior art to establish how one might determine PAI-1 promoter genotype using a protein sample.

The unpredictability of associating PAI-1 genotype with exercise-induced increases in fibrinolysis and the required effects such as preventing or ameliorating cardiovascular disease is exemplified by Tiyasangthong (2001). Tiyasangthong examine the hypothesis that exercise training affects fibrinolytic variables (p.103), and that the changes in PAI-1 activity with exercise training is related to PAI-1 polymorphisms (p.107). The reference indicates that there are only significant changes in t-PA activity in heterozygous 4G/5G genotypes, and in t-PA antigen in the homozygous 4G/4G genotypes (Table 7). However, the claims drawn to methods for preventing cardiovascular disease may be considered as encompassing those methods which completely keep even the most minor forms of cardiovascular disease from

occurring; wherein the pertinent method step is engaging a subject in exercise training. And while there may be an inverse relationship between physical activity and the risk of developing cardiovascular disease, the prior art of Sesso et al (2000) indicates that participation in physical exercise is not sufficient to provide a guaranteed prevention of any form or type of cardiovascular disease (Table 2; p.976, right col., lns.44-53). Similarly, while measures of variables that are associated with the fibrinolytic system (i.e. t-PA activity and t-PA antigen concentration) are provided in the Examples of the specification, there is no indication that even the detected increase in t-PA activity shown in Table 1 is in fact sufficient to in any way ameliorate cardiovascular disease.

Further it is noted that the claims have been amended to recite a "sample comprises a nucleic acid or protein from the subject". However, as the relevant polymorphism is in the promoter of the PAI-1 gene, it is entirely unpredictable as to how a protein sample might be used in the detection of the promoter genotype.

Quantity of experimentation required

There would be a large amount of experimentation required to make and use the invention in the full scope as claimed. One would have to conduct a large case-control experimentation to determine if any exercise in fact prevents cardiovascular disease or ameliorates disease. The fact that measures of t-PA activity and t-PA antigen are not necessarily indicative of those requirements is supported by the conclusions of Womack et al (2001), which teaches, in regards to individuals whose t-PA increased with exercise, "further research is needed to better understand the mechanisms underlying the sustained enhanced fibrinolysis profile, and to determine whether exercise training

improves fibrinolysis in this population". Such a study may or may not indicate that there is a reliable and statistically significant exercise dependent increase in prevention of cardiovascular disease, or amelioration of cardiovascular disease, that is associated with a subject's PAI-1 genotype in any particular population.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and the breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the amount of guidance by the applicant and the paucity of working examples, it is the conclusion the an undue amount of experimentation would be required to make and use the invention claimed invention in the full scope of the claims.

Response to Remarks

Applicant has traversed the rejection of claims under 35 USC 112 1st¶ for lack of enablement (pages 6-8 of the Remarks of 08/06/2009). Applicants' arguments have been fully and carefully considered but are not found to be persuasive to fully withdrawn the rejection. It is noted that the rejection as set forth in this Office Action has identified scope that is enabled by the specification.

Initially it is noted that the portions of the rejection dealing with particular amounts of exercise (e.g. the requirement in the enabled scope for moderate exercise) has been withdrawn from the instant rejection.

Applicants have argued, in response to the rejection of claims drawn to elements of preventing and ameliorating cardiovascular disease, that Applicants need nod provide evidence of an association between exercise and these elements as the specification recites that there is a link between t-PA activity and antigen and fibrinolysis, and there is also a link between fibrinolysis and alleviated symptoms of cardiovascular disease. And while Applicants assert that MPEP 2107 require that the Examiner accept Applicants statements as true, the Examiner maintains that the instant rejection sets forth a reasonable argument that the mere alteration of the measured parameters analyzed in the specification is not in fact evidence of the required physiological results of the rejected claims. The Examiner maintains that there are in fact no results in the instant specification with regard to prevention of cardiovascular disease or amelioration of cardiovascular disease.

The rejection as set forth is **MAINTAINED.**

Maintained Claim Rejections - 35 USC § 102

It is noted the examined claims of the instant application, rejected in this section of the Office Action as anticipated by the prior art, have been previously rejected in this Office action under 35 USC 112 1st ¶ as lacking enablement (i.e. a scope of enablement rejection). The prior art cited in this rejection teaches all of the steps of the claimed methods, and meets all of the limitations of the rejected claims. While the cited prior art anticipates an embodiment of the claims, it is does not enable the claims as addressed in the rejection of claims under 35 USC 112 1st ¶. Further it is noted that the specification of the instant application cannot be considered enabling for the methods of the prior art because the instant application does not present the same data, gathered from the same population, as the prior art.

3. Claims 1-18, 28, and 29 rejected under 35 U.S.C. 102(b) as being anticipated by Väisänen et al (1999) as cited in the IDS.

With regard to independent claims 1, 7, 13, and 28 Väisänen et al teaches methods comprising the steps of providing a sample comprising nucleic acid from the subject, and detecting the genotype of a subject with respect to the 4G/5G PAI-1 gene promoter polymorphism (p.1118, left col., DNA analysis). The methods of Väisänen et al utilize the identification of subjects with 4G/4G, 4G/5G, and 5G/5G genotypes (Table 1), thus identifying subjects with at least one 4G allele as required by claims 1, 7, and 13, and subjects with two 4G alleles as required by claim 28. Further, the reference teaches engaging the subject in an exercise program (p.1118, left col., Cardiorespiratory fitness and exercise intervention), where the subjects of the scientific study are advised to perform a certain training program. With regard to the requirements that the exercise is of a period of time sufficient to decrease t-PA antigen (claims 1-18) or increase t-PA activity, The MPEP in chapter 2100 states:

> Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

In the examination of the instant application, based on the teachings of the instant specification and the arguments of 02/05/2008 and 08/06/2009 as presented by Applicants, the PTO has basis for believing that the exercise of Väisänen et al meets the limitations of the claims. Further, because the exercise of Väisänen et al is for the

required period of time, the exercise prevents cardiovascular disease (claims 7-12) and ameliorates cardiovascular disease (claims 13-18 and 29). Where claims 13-18 and 29 require subject suffering from cardiovascular disease, it is noted that the specification provides no limiting definition or guidance as to what is required for any individual to be 'suffering from cardiovascular disease'. As such, 'cardiovascular disease' is considered to be any amount of fibrin in the cardiovascular system, where the subjects of Väisänen et al would thus meet this interpretation of the term as in a population of individuals as taught by Väisänen et al at least some of the individuals would have some fibrin in their cardiovascular system.

Regarding claims 2, 3, 8, 9, 14, and 15, Väisänen et al teaches the analysis of subjects that were heterozygous (4G/5G) and homozygous for the 4G allele (4G/4G) at the promoter polymorphic site (p.1118, right col., lns.10-35), and that subjects from both of these groups responded to the exercise intervention (Table 1).

Regarding claims 4-6, 10-12, and 16-18, Väisänen et al teaches the particular nature of the exercise training with regards to duration of the regimen (p.1117, right col., Study design) and courses of exercise (p.1118, left col., Cardiorespiratory fitness and exercise intervention). The reference teaches that the study took place over three years, with exercise occurring three times a week for the first three months, followed by five times a week there after. This meets the definition of extensive exercise as defined in the specification (paragraph [0019]) as the exercise regimen of Väisänen et al includes at least 25 single courses of exercise, and takes place over about 400 days. Relevant to claims 6, 7, 11, 12, 17 and 18, because of the progressive nature of the

definitions of limited and moderate exercise as defined in the instant specification (paragraphs [0020]-[0021]), the exercise of Väisänen et al would necessarily be comprised of both limited and moderate exercise.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 102 as anticipated by the cited prior art. Applicants' remarks (p.8-9 of the Remarks of 08/06/2009) have been fully and carefully considered but are not found to be persuasive to withdraw the rejection. Applicants argue (p.9 of the Remarks) that Vaisanen does not teach that placing a person with at least one 4G allele on an exercise regimen will benefit that person more that a person who is homozygous 5G. The argument is not persuasive. The examiner maintains that the cited reference teaches all of the steps of the claims, where if, as Applicants assert, a 4G subject will benefit from exercise more that a 5G homozygous subject, then any 4G subjects of the prior art will in fact have that same increased benefit.

The rejection as set forth is **MAINTAINED.**

Conclusion

4. No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Stephen Kapushoc/
Primiary Examiner, Art Unit 1634